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Mechanism of development of pre-eclampsia linking breathing disorders to endothelial dysfunction

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SUMMARY

High blood pressure is an important component of pre-eclampsia. The underlying mechanism of development of hypertension in pre-eclampsia is complicated and still remains obscure. Several theories have been advanced including endothelial dysfunction, uteroplacental insufficiency leading to generalized vasoconstriction, increased cardiac output, and sympathetic hyperactivity. Increased blood flow and pressure are thought to lead to capillary dilatation, which damages end-organ sites, leading to hypertension, proteinuria and edema. Additional theories have been put forward based on epidemiological research, implicating immunological and genetic factors. None of these theories have been substantiated. Based on a review of literature this paper postulates that the initiating event for the development of pre-eclampsia is intermittent hypoxia associated with irregular breathing during sleep, hypoapnea, apnea, inadequate respiratory excursions during the waking hours and inadequate cardiopulmonary synchronization (abnormal sympatho-vagal balance).

Background

Despite being one of leading causes of maternal death and a major contributor of maternal and perinatal morbidity, the mechanism responsible for the pathogenesis of pre-eclampsia remains unclear [1,2]. Evidence shows that inadequate oxygenation from various causes leads to the initiation of an abnormal autonomic response. Several studies show a strong association between obstructive sleep apnea (OSA) and hypertension in the non-pregnant state [3,4]. Few studies in pregnancy corroborate this finding [5,6]. Nocturnal hypertension is observed significantly more in patients who have pre-eclampsia than those with gestational hypertension or chronic hypertension [5]. Also in OSA there is relative increase of the sympathetic activity associated with vasospasm, endothelial dysfunction, and increased angiotensin II levels, findings that are also implicated in the pathogenesis of pre-eclampsia [7,8].

Incidence of snoring, hypoapnea and sleep apnea in the non-pregnant state, pregnancy and pre-eclampsia

The incidence of snoring, hypoapnea, and sleep apnea is 9% in non-pregnant females and 14% in pregnant women [9–11]. By the third trimester, 24% of women were reported to have a snoring problem (symptom of sleep apnea). Habitual snorers had a higher frequency of pregnancy-induced hypertension (14%) compared to 6% of non-habitual snorers. The intrauterine growth retardation incidence was 7% in habitual snorers compared to 2.6% in non-snorers [10]. In this study it was noted that all subjects who habitually snored and developed pre-eclampsia started to snore before hypertension or proteinuria was present. Abnormalities of breathing such as inspiratory flow limitation are observed more frequently in patients with pre-eclampsia (31 ± 8%) as compared to normal pregnant women (15.5 ± 2.3%), and non-pregnant females (<5%) [9]. The autonomic imbalance associated with this abnormal breathing was found to be associated with high systolic and diastolic blood pressure [9].

In studies conducted with patients having OSA, continuous positive airway pressure (CPAP) treatment resulted in decreased nocturnal blood pressure further confirming a causal relationship between the breathing disorder and hypertension [16]. Chronic hypertensive patients who are at higher risk of pre-eclampsia due to associated chronic snoring have improved blood pressure control and decreased incidence of pre-eclampsia when nasal CPAP treatment is used in early pregnancy [17]. Patients with pre-eclampsia are noted to have a higher incidence of upper airway obstruction [18]. OSA is not only associated with autonomic imbalance and increased sympathetic activity, but is also known to be associated with vascular endothelial dysfunction, increased oxidative stress, inflammation, and platelet agglutination leading to

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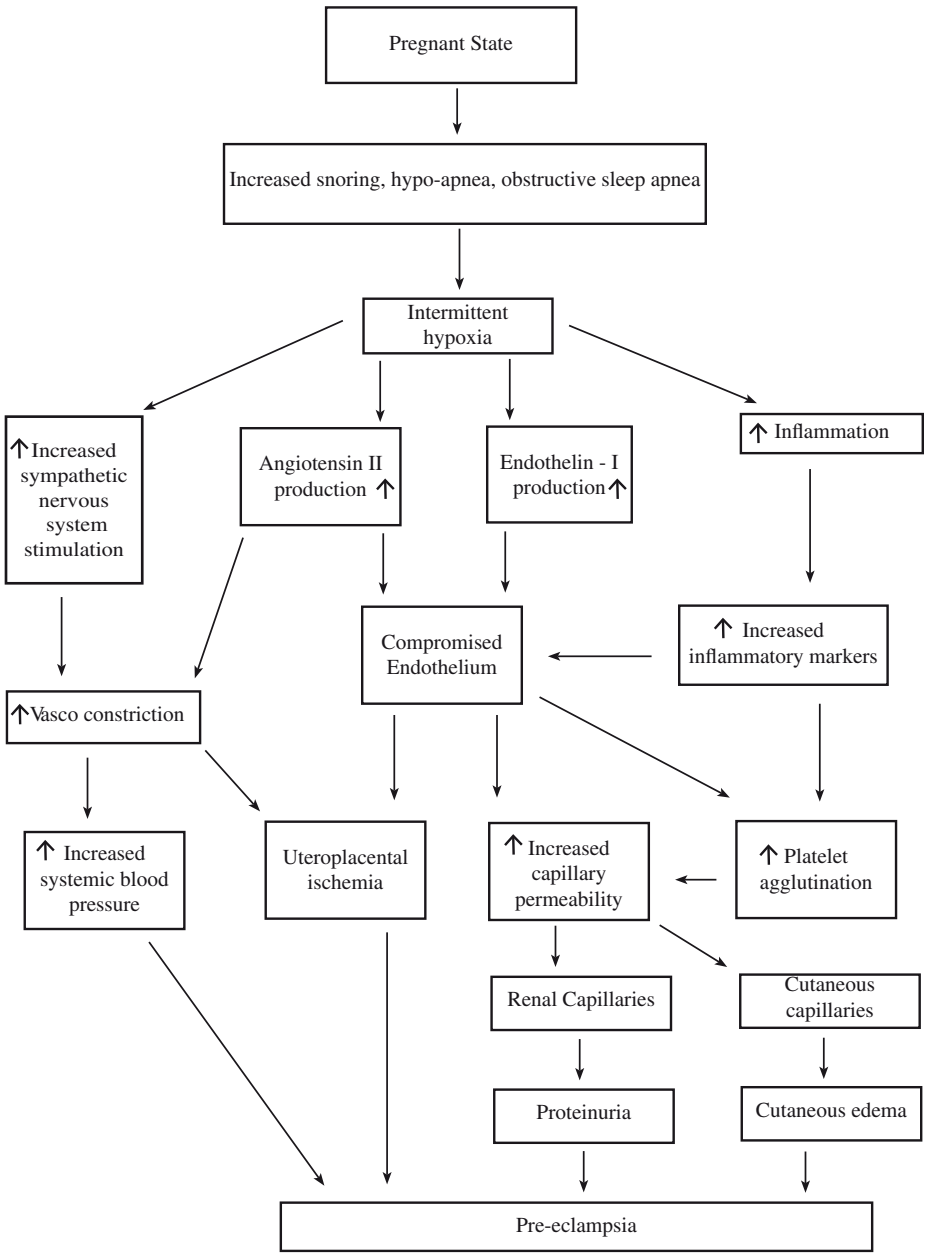

Fig. 1. Hypothesized pathways by which hypoapnea and sleep apnea in pregnancy leads to the pre-eclampsia syndrome. Sleep-disordered breathing leads to intermittent hypoxia (Fig. 1) [3,6]. Intermittent hypoxia causes increased sympathetic nervous system stimulation, angiotensin II production and altered vasoconstrictor activity [12,13]. Increased vasoconstrictor activity leads to hypertension [12,13]. Intermittent hypoxia leads to endothelin-1 production which is associated with endothelial dysfunction and vasoconstriction [6]. Inflammatory markers are increased [14,15]. Both endothelin-1 and inflammatory markers increase leading to increased platelet agglutination, compromised endothelial function and increased capillary permeability [14,15]. This leads to edema (cutaneous capillary involvement) and to proteinuria (glomerular capillary involvement). Hypertension develops from increased sympathetic tone and increased levels of endothelin-1. Capillary involvement of uterine and placental vessels lead to placental dysfunction.

initiation and progression of cardiac and vascular disease [4]. In the non-pregnant state, there is a strong association between OSA, increased sympathetic activity and hypertension [3,7]. Also at high altitude where oxygen levels are low, the respiratory excursions are unable to deliver adequate oxygen, which might explain higher incidence of pre-eclampsia [19].

Obstructive sleep apnea and abnormal renin–angiotensin system

Pre-eclamptic patients are observed to have an abnormal renin–angiotensin system [20]. There is a significant interaction between angiotensin-converting enzyme gene insertion/deletion polymorphism and OSA, suggesting another mechanism for the development of hypertension [21]. Chronic induced intermittent hypoxia (CIHO) in rats can cause levels of circulating renin activity and angiotensin II to increase, which suggests that an activated renin–angiotensin system may contribute to the pathogenesis of CIHO-induced hypertension [22].

Obstructive sleep apnea associated with endothelial function index and vascular spasms

Pre-eclampsia is known to be associated with vasoconstriction. Mechanical properties of vessels are abnormal in pre-eclamptic patients. Flow-meditated dilation is decreased in pre-eclamptic wo-

men [23]. A study conducted in OSA patients revealed that CPAP treatment restored the compromised flow-mediated dilation [24]. In a study comparing normal pregnant with pre-eclamptic patients the latter had higher respiratory disturbance index during sleep and lower endothelial function index [6].

Relationship of autonomic nervous system to normal and abnormal respiration in the non-pregnant, normal pregnant and pre-eclampsia condition

The autonomic (sympatho-vagal) balance is strongly associated with respiration [25]. Increased vagal (parasympathetic) tone is associated with slow breathing and increased tidal volume, while irregular shallow fast breathing is associated with increased sympathetic tone [25–27]. Studies on both normotensive pregnant and pre-eclamptic women have shown that the vagal response (parasympathetic tone) is decreased in pre-eclampsia [28]. Other studies have concluded that both sympathetic and vagal responses are increased in pre-eclampsia [29]. Pre-eclamptic women have an autonomic imbalance associated with an increase in sympathetic nervous tone, increased heart rate, and hypertension as compared to normal pregnant women [30,31].

Decrease in incidence of pre-eclampsia and improvement of hypertension, with restoration of normal breathing and relaxation exercises

Another line of evidence supporting this theory is the decrease in the incidence of pre-eclampsia following the restoration of normal breathing. In a study by DiPietro et al. induced maternal relaxation during 32nd week of pregnancy resulted in significant changes in maternal heart rate, skin conduction and increased respiratory sinus arrhythmia. Parallel significant alterations of fetal neural behavior were observed including decreased fetal heart rate, and increased fetal heart rate variability with increased fetal movement-heart rate coupling [30]. Studies conducted on pregnant patients with abnormal umbilical artery Doppler findings demonstrated significantly improved blood flow as measured by the velocitometry parameters when yoga was practiced with deep slow breathing techniques [32]. A case-controlled prospective study of 355 pregnant women who practiced a slow, deep breathing-based yoga technique starting at 18–20 weeks showed significantly decreased incidence of pre-term birth and pre-eclampsia [33].

Summary

There is strong evidence to support the notion that pre-eclampsia is initiated by dysarrhythmic respiration. Either orthostatic stress-induced respiratory changes or sleep apnea or combination of both elicit imbalance of autonomic nervous system towards sympathetic state. The resultant abnormal cardiopulmonary synchronization significantly diminishes vagal balance. The imbalance leads to vascular changes in the mother, fetus and placenta. The cycle of intermittent anoxia from sleep-associated apnea and daytime abnormal cardiopulmonary synchronization leads to vascular damage, and alterations in the renin–angiotensin system as the pregnancy advances. In the mother, pre-eclampsia clinically presents with hypertension, edema and proteinurea, while in the fetus there is diminished placental blood flow and clinical evidence of utero-placental insufficiency. The use of CPAP treatment for apnea reverses the blood pressure elevation in pregnant and non-pregnant states while voluntary deep slow breathing relaxation exercise promotes vagal balance leading to decreased incidence of pre-eclampsia. Bed-rest is very helpful as it allows for diminishing orthostatic stress and allows better expansion of lungs and oxygenation in pregnancy.

Conclusion

Based on various epidemiological, experimental animal studies and sleep studies we cited in this article it appears that there is strong evidence that disordered breathing is an important pathogenic mechanism for the development of pre-eclampsia. This is further supported by the evidence cited that the correction of disordered breathing results in the decreased incidence of pre-eclampsia. While these findings are supportive they cannot prove a causal relationship. Further controlled prospective studies are needed to confirm this hypothesis.

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